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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/993,647	11/27/2001	Bernd Riedl	BAYER 18A	1010

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EXAMINER	
RAO, DEEPAK R	

ART UNIT	PAPER NUMBER
1624	

DATE MAILED: 06/03/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/993,647	RIEDL ET AL.	
	Examiner	Art Unit	
	Deepak R Rao	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 March 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *68,74,80,81,87 and 93* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *68,74,80,81,87 and 93* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *123002*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

This office action is in response to the communication received on March 17, 2004.

Claims 68, 74, 80, 81, 87 and 93 are pending in this application.

The following rejections are maintained:

1. Claims 74, 80, 81, 87 and 93 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the treatment of carcinoma of colon, does not reasonably provide enablement for all other diseases mediated by raf kinase. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. The reasons provided in the previous office action are incorporated here by reference.

Applicant's arguments have been fully considered but they were not deemed to be persuasive. Applicant argues that 'no evidence supporting the non-enablement rejection has been provided'. However, it was clearly explained in the previous office action that the claims are drawn to several types of cancers affecting different organs and having diffcrent methods of growth or harm to the body, and differcnt vulnerabilities. The development of the most efficacious strategy for the treatment of cancers is based on understanding the underlying mechanisms of carcinogenesis. This includes the knowledge that the carcinogenic process is a multi-step, multi-mechanism process and that no two cancers are alike, in spite of some apparent universal characteristics, such as their inability to have growth control, to terminally differentiate, to apoptose abnormally and to have an apparent extended or immortalized life span. Since tumor promotion phase involves multiple mechanisms, there is no existence of a single

therapeutic approach. The instant claims recite 'solid cancers, carcinomas, myeloid disorders or adenomas' as the cancers 'mediated by raf kinase', however, the art does not identify a single class of compounds that can treat all these types of cancers generally. Further, one skilled in the art of cancer therapy recognizes that there are complex interactions between individual genetic, developmental state, sex, dietary, environmental, drug, and lifestyle factors that contribute to the carcinogenic process, making it even more challenging to have a single therapeutic agent for the treatment of diverse cancers. For example, breast cancer is quite different from liver cancer and even not all breast cancers are identical to each other. Rigorously planned and executed clinical trials, incorporating measurement of appropriate biomarkers and pharmocodynamic endpoints are critical for selecting the optimal dose and schedule. A detailed understanding of the molecular mode of action of the raf kinase inhibitors alongside the elucidation of the molecular pathology of individual cancers is required to identify tumor types and individual patients that may benefit most from treatment. It is also important to construct a pharmacologic audit trail linking molecular biomarkers and pharmacokinetic and pharmacodynamic parameters to tumor response endpoints. There are cancers where the skill level is high and there are multiple successful chemotherapeutic treatments. In many, many cancers, however, there is no chemotherapy whatsoever available and therefore, no chemotherapy is available. This establishes the difficulties involved in the treatment of cancers. The various references of record and those presented at the interview have been considered, however, it is maintained that applicants have not provided sufficient test assays or data to support the method of treatment commensurate in scope with the claims, as of the filing date of the application.

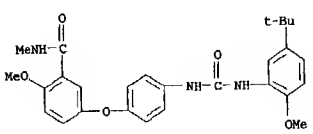
2. Claim 68 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The preamble "One or more compounds which are:" is confusing.

Applicant submits that 'the claim language is intended to encompass the five compounds individually as well as mixtures thereof'. The following claim language is suggested for the claim: "A compound selected from: … … or a mixture thereof".

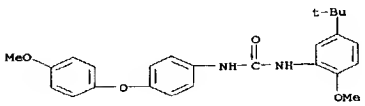
3. Claims 68, 74, 80, 81, 87 and 93 are rejected under 35 U.S.C. 103(a) as being unpatentable over Miller et al., WO 99/32463, for the reasons provided in the previous office action which are incorporated here by reference.

Applicant's arguments have been fully considered but they were not deemed to be persuasive. Applicant argues that the reference does not provide any direction to make the selections necessary to arrive at the claimed compounds. This is not found to be persuasive because the reference clearly teaches the genus encompassing the claimed species and further expressly provides compounds that are structurally analogous to the claimed compounds. See for example, compound 34 in page 73, which differs from the instantly claimed compound of N-(5-tert-butyl-2-methoxyphenyl)-N'-(4-(4-methoxy-3-(N-methylcarbamoyl)phenoxy)phenyl)urea, (the first compound in claim 64) by the –C(=O)-NHMe substituent on the terminal phenyl group.

Claimed compound:



Reference compound 34:



Similarly, the second claimed compound is structurally analogous to compound 101 (page 79) of the reference. The reference clearly provides that the aromatic ring (i.e., phenyl, pyridinyl, etc.) can be substituted by Z_{n1} wherein n1 is 0 to 3 and Z definition includes $-C(O)NR^7R^7$ wherein R^7 is H, alkyl, etc. see page 9, lines 1-9. Further, the reference also provides a compound wherein the phenyl is substituted by –C(O)NHMe group, see page 16, lines 6-7. Therefore, contrary to applicant's arguments, the reference clearly teaches compounds that are structurally analogous to the instantly claimed compounds and thus, the reference provides sufficient motivation to one of ordinary skill in the art to prepare compounds having the N-methylcarbamoyl substituent.

Further, applicant argues that the claimed compounds have distinct activity of inhibiting raf kinase as compared to p38 kinase activity disclosed for the reference compounds. However, the prior art need not disclose the newly discovered property in order for there to be a *prima facie* case of obviousness. In fact, similar properties may normally be presumed when compounds are very close in structure. Also note, there is no requirement that the prior art must suggest that the claimed compound will have the same or similar utility as that discovered by applicant in order to support a legal conclusion of obviousness. *In re Dillon*, 919 F.2d 688, 696, 16 U.S.P.Q.2d 1897, 1904 (Fed. Cir. 1991). If the prior art compound does in fact possess a particular benefit, even though the benefit is not recognized in the prior art, applicant's recognition of the benefit is not in itself sufficient to distinguish the claimed compounds from the prior art. Note that the reference teaches that the compounds have p38 kinase inhibitory properties and further, that the compounds are useful in the treatment of diseases including cancer (see pages 6-7), which is sufficient to one of ordinary skill to make the claimed compounds because similar properties are normally presumed when compounds are very close in

structure. There is nothing on the record to show that the reference compounds do not possess the activity of the instant compounds. Applicants must prove that their compounds possess a property that the prior art compounds do not possess. The discovery of additional use not disclosed in the reference does not make otherwise obvious compounds unobvious. See *In re Best*, 195 USPQ 430 (CCPA 1977). The PTO can require an applicant to prove that the relevant prior art products do not necessarily or inherently possess characteristics of the claimed product.

4. Claims 68, 74, 80, 81, 87 and 93 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 68-98 of copending Application No. 10/042,203, for the reasons provided in the previous office action which are incorporated here by reference.

Applicant argues that the reference claims are directed to pharmaceutically acceptable salts of the urea compounds recited in instant claim 68. However, the salt of a compound is obvious over the compound itself unless there are unexpected properties. Accordingly, the rejection has been maintained.

Receipt is acknowledged of the Information Disclosure Statement filed on December 30, 2002 and a copy is enclosed herewith. The citations listed as "A Notice of References Cited" from various applications and International Search Reports for various PCT and EP applications (see pages 6-8) are crossed off as these do not represent proper publications *per se* that comply with the requirements of 37 CFR 1.97 and 1.98 and therefore, will not appear on the patent as a cited document.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Deepak Rao whose telephone number is (571) 272-0672. The examiner can normally be reached on Tuesday-Friday from 6:30am to 5:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Mukund Shah, can be reached on (571) 262-0674. If you are unable to reach Dr. Shah within a 24 hour period, please contact James O. Wilson, Acting-SPE of 1624 at (571) 272-0661. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571) 272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Deepak Rao
Primary Examiner
Art Unit 1624

May 27, 2004